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Hospital-based collaboration for epidemiological investigation of vaccine safety: a potential solution for low and middle-income countries?

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As each national immunization program matures with increasing uptake of vaccines in the population and control of their targeted vaccine-preventable diseases (VPD), vaccine safety concerns become more prominent. Such concerns are frequently a mix of coincidental adverse events falsely attributed to the memorable immunization event and real vaccine-induced reactions.(1) (2) Sorting the two types of concerns out requires implementation of appropriate surveillance systems for adverse events following immunizations (AEFI)s, and timely and rigorous scientific assessment (and occasionally good media skills) to maintain public confidence in immunization programs.(3) Failures to do so have tragically resulted in resurgence of VPD's in multiple countries. (4) (5).

Traditionally, in high income countries, large populations with computerized databases that link vaccination history exposures and medical visits have been used for rigorous testing of hypothesized vaccine safety concerns raised by passive surveillance systems for AEFI's.(6, 7) Pilot projects for similar large linked databases (LLDB) in low and middle-income countries (LMIC)'s have begun, but are not without problems.(8) Given the major challenges in obtaining the substantial resources needed to develop and sustain such LLDB's,(9) affordable, timely and reliable alternative solutions for LMICs (even if imperfect) are needed. This need is highlighted by the accelerated introduction of new vaccines for diseases endemic in LMICs (e.g., Meningitis A, Rotavirus, Cholera and Dengue) without prior use in countries with strong pharmacovigilance systems. (10)

In an earlier review, we noted the potential for an international collaboration of referral hospitals in LMICs to help meet this need, building on the model of a similar successful collaboration of 15 high and middle income countries to assess the risk of a rare serious AEFI (Guillain Barré Syndrome) following Influenza A (H1N1) 2009 monovalent vaccines.

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(10) (11) In this issue of Vaccine, Drs. Perez-Vilar, Maure, Bravo and collaborators from the World Health Organization (WHO), the Pan-American Health Organization (PAHO), Erasmus University and 26 large referral hospitals in 16 countries [many from low and middle income countries (LMICs)] from all WHO regions present the promising results and lessons learned from a proof of concept implementation of such an expanded hospital-based collaboration. (12–14) Under a common protocol for data collection and analysis, they replicated much of the epidemiologic evidence for two previously known vaccine adverse events commonly requiring hospitalization: immune thrombocytopenic purpura (ITP) and aseptic meningitis (AM) following administration of measles-mumps-containing vaccines.

Their choice of self-controlled case series (SCCS) for the study analyses permitted them to implicitly control for time-fixed confounders while maximizing study efficiency.(15–17) This approach also averted the need to identify population denominators which, at least in LMICs, are difficult to obtain and, when available, often unreliable - albeit at the price of inability to directly assess the attributable risk. Highlighting the validity of this approach (and the relative stability of study findings of rare outcomes among large denominators), the team successfully confirmed the previously known overall elevated risks of ITP and AM. Moreover, given the different measles and mumps vaccine strains used across the 16 study countries, the study also suggests potential differences in relative risk between different measles-mumps vaccine strains for both ITP and AM, including a potential new signal for AM risk with a locally-produced Hoshino mumps vaccine. (18) (19–21)

Further studies will be needed to validate whether these observed differences are real or artifactual (e.g., due to differences in implementation of protocols in each country). Nevertheless, these findings highlight the importance and value of post-marketing surveillance for vaccines and other pharmaceutical products in LMIC's overall. (9) This is especially important since LMIC's are where the largest number of pediatric immunizations occur globally. (22) While much of these vaccines are supplied via Global Alliance for Vaccines and Immunizations (GAVI) or UNICEF, requiring pre-qualification by WHO to meet international standards(23), some vaccines are likely to be supplied by domestic manufacturers who may or may not meet international standards.(24)

While this proof of concept study looks promising, it is important to keep the following caveats/lessons in mind. First, the study addresses two events, ITP and AM, already known to be associated with MMR vaccines. For a newly introduced vaccine, active surveillance systems such as the hospital-based system proposed in this proof-of-concept study could be useful mainly to evaluate a limited number of pre-specified safety signals using a common protocol. Such signals could be identified during by the pre-licensure trials, by analyzing passive AEFI surveillance, , case reports, safety experience with similar vaccines, or to respond to public concern. Otherwise, otherwise, identifying which AEFI to study and developing a common protocol could be more complex.

Secondly, once an event is found to be associated with vaccination, the attributable risk (AR) of the AEFI for a vaccine is important for risk-benefit decisions. In settings where high quality routine population-based vaccine coverage estimates are available (e.g., United States and United Kingdom), it is possible to combine that with the RR from SCCS to

calculate an accurate AR. (25) Unfortunately, most LMIC rely on less precise administrative data to estimate their vaccine coverage with periodic 30 cluster surveys as backup.(22) Thus, while some kind of “back of envelope” estimate of AR is possible, it is likely to be more imprecise than validation studies in high income countries. This is by no means a fatal weakness, however, and highlights the limitations of working with less-than-ideal data. Also, once an association is confirmed, follow-up studies to estimate the AR can be performed.

Thirdly, it would be important to routinely include a negative “control” outcome in future studies using this approach. It provides an important data quality control tool and a potential way to “standardize” rates across diverse geographical sites despite inherent differences in referral patterns, medical practices, etc. This would improve data interpretation when inevitable differences in AEFI’s studied are observed.

Fourthly, given that cases of AEFI from only a sample of referral hospitals in a country are used in this approach, the potential for selection and information bias related to vaccine exposure should be considered. (26)

The potential limitations described above should not distract from recognizing the unique achievements of a project which has succeeded in confirming the risk of two rare and difficult to diagnose AEFIs, using a common SCCS protocol, with strong participation from LMICs. The authors, appropriately, chose to prioritize recruitment of large referral hospitals with medical specialties and easy access (ideally electronic) to vaccination records, to facilitate the accurate identification of rare and difficult to diagnose events following vaccination.(12–14) Finally, although cost estimates have not been provided, both the proof of concept study published in this issue (12–14) and the international GBS investigation which served as precursor for this study,(11) have been implemented by WHO mainly with limited financial support from the U.S. Food and Drug Administration (FDA). The challenge now is to find sustainable funding for the post-licensure active investigation of vaccine (and, possibly, also drug) adverse events, so the promise of future vaccines in LMIC’s can be fulfilled.(27) Such a system, if properly designed, could also facilitate the evaluation of the effectiveness (and by extension also risk-benefit) of any intervention for the control of serious diseases prevalent in LMICs.(28)

References

1. Chen RT, Rastogi SC, Mullen JR, Hayes SW, Cochi SL, Donlon JA, et al. The Vaccine Adverse Event Reporting System (VAERS). Vaccine. 1994;12(6):542–50. [PubMed: 8036829]
2. Chen RT, Shimabukuro TT, Martin DB, Zuber PL, Weibel DM, Sturkenboom M. Enhancing vaccine safety capacity globally: A lifecycle perspective. Vaccine. 2015;33 Suppl 4:D46–54. [PubMed: 26433922]
3. Ellenberg SS, Chen RT. The complicated task of monitoring vaccine safety. Public Health Rep. 1997;112(1):10–20; discussion 1. [PubMed: 9018282]
4. Gangarosa EJ, Galazka AM, Wolfe CR, Phillips LM, Gangarosa RE, Miller E, et al. Impact of anti-vaccine movements on pertussis control: the untold story. Lancet. 1998;351(9099):356–61. [PubMed: 9652634]
5. Bonanni P, Zanella B, Santomauro F, Lorini C, Bechini A, Boccalini S. Safety and perception: What are the greatest enemies of HPV vaccination programmes? Vaccine. 2017.

6. McNeil MM, Gee J, Weintraub ES, Belongia EA, Lee GM, Glanz JM, et al. The Vaccine Safety Datalink: successes and challenges monitoring vaccine safety. Vaccine. 2014;32(42):5390–8. [PubMed: 25108215]
7. Hviid A Postlicensure epidemiology of childhood vaccination: the Danish experience. Expert Rev Vaccines. 2006;5(5):641–9. [PubMed: 17181438]
8. Ali M, Canh GD, Clemens JD, Park JK, von Seidlein L, Minh TT, et al. The use of a computerized database to monitor vaccine safety in Viet Nam. Bull World Health Organ. 2005;83(8):604–10. [PubMed: 16193545]
9. Foundation G. A report of the safety and surveillance working group 2011 [Available from: https://docs.gatesfoundation.org/documents/SSWG%20Final%20Report%2011%2019%2013_designed.pdf.
10. Izurieta HS, Zuber P, Bonhoeffer J, Chen RT, Sankohg O, Laserson KF, et al. Roadmap for the international collaborative epidemiologic monitoring of safety and effectiveness of new high priority vaccines. Vaccine. 2013;31(35):3623–7. [PubMed: 23707171]
11. Dodd CN, Romio SA, Black S, Vellozzi C, Andrews N, Sturkenboom M, et al. International collaboration to assess the risk of Guillain Barre Syndrome following Influenza A (H1N1) 2009 monovalent vaccines. Vaccine. 2013;31(40):4448–58. [PubMed: 23770307]
12. Sea Perez-Vilar. Enhancing global vaccine pharmacovigilance: Proof of concept on aseptic meningitis and immune thrombocytopenic purpura following measles-mumps vaccination Vaccine. 2017.
13. Maure C ea. Operational Lessons Learned in conducting a multi-country collaboration for vaccine safety signal verification and hypothesis testing: The Global Vaccine Safety Multi Country Collaboration initiative. Vaccine. 2017.
14. Bravo PP-VS, et al. Building capacity for active surveillance of vaccine adverse events in the Americas: a hospital-based multi-country network. Vaccine, in press. 2017.
15. Whitaker HJ, Farrington CP, Spiessens B, Musonda P. Tutorial in biostatistics: the self-controlled case series method. Stat Med. 2006;25(10):1768–97. [PubMed: 16220518]
16. Weldeselassie YG, Whitaker HJ, Farrington CP. Use of the self-controlled case-series method in vaccine safety studies: review and recommendations for best practice. Epidemiol Infect. 2011;139(12):1805–17. [PubMed: 21849099]
17. Farrington CP. Control without separate controls: evaluation of vaccine safety using case-only methods. Vaccine. 2004;22(15–16):2064–70. [PubMed: 15121324]
18. Dorreh FHM. Adverse events associated with MMR vaccines in Arak. Journal of Iranian Clinical Research. 2015;1:6–10.
19. Esteghamati A, Keshtkar A, Heshmat R, Gouya MM, Salar Amoli M, Armin S, et al. Adverse reactions following immunization with MMR vaccine in children at selected provinces of Iran. Arch Iran Med. 2011;14(2):91–5. [PubMed: 21361714]
20. Ueda K, Miyazaki C, Hidaka Y, Okada K, Kusuhara K, Kadoya R. Aseptic meningitis caused by measles-mumps-rubella vaccine in Japan. Lancet. 1995;346(8976):701–2.
21. Sood A, Mitra M, Joshi HA, Nayak US, Siddaiah P, Babu TR, et al. Immunogenicity and safety of a novel MMR vaccine (live, freeze-dried) containing the Edmonston-Zagreb measles strain, the Hoshino mumps strain, and the RA 27/3 rubella strain: Results of a randomized, comparative, active controlled phase III clinical trial. Hum Vaccin Immunother. 2017:1–8.
22. Casey RM, Dumolard L, Danovaro-Holliday MC, Gacic-Dobo M, Diallo MS, Hampton LM, et al. Global Routine Vaccination Coverage, 2015. MMWR Morb Mortal Wkly Rep. 2016;65(45):1270–3. [PubMed: 27855146]
23. Organization WH. World Health Organization Prequalification.
24. Luter N, Kumar R, Hozumi D, Lorenson T, Larsen S, Gowda B, et al. An updated methodology to review developing-country vaccine manufacturer viability. Vaccine. 2017;35(31):3897–903. [PubMed: 28602604]
25. Stowe J, Andrews N, Ladhani S, Miller E. The risk of intussusception following monovalent rotavirus vaccination in England: A self-controlled case-series evaluation Ref. No: JVAC-D-16–01124. Vaccine. 2016;34(50):6115. [PubMed: 27899199]

26. Sturkenboom MC. The narcolepsy-pandemic influenza story: can the truth ever be unraveled? Vaccine. 2015;33 Suppl 2:B6–B13. [PubMed: 26022571]

27. Black S, Mulholland K, Halsey NA. Developing sustainable funding for vaccine safety infrastructure. Vaccine. 2010;28(5):1133–4. [PubMed: 19945416]

28. Heininger U, Holm K, Caplanusi I, Bailey SR, Safety CWGoV. Guide to active vaccine safety surveillance: Report of CIOMS working group on vaccine safety - executive summary. Vaccine. 2017;35(32):3917–21. [PubMed: 28645716]